Clinicopathologic Features of *BRCA*-Linked and Sporadic Ovarian Cancer

Jeff Boyd, PhD

Yukio Sonoda, MD

Mark G. Federici, MS

Faina Bogomolniy, BS

Esther Rhei, MD

Diane L. Maresco, PhD

Patricia E. Saigo, MD

Lois A. Almadrones, RN

Richard R. Barakat, MD

Carol L. Brown, MD

Dennis S. Chi, MD

John P. Curtin, MD

Elizabeth A. Poynor, MD

William J. Hoskins, MD

Context Most hereditary ovarian cancers are associated with germline mutations in *BRCA1* or *BRCA2*. Attempts to define the clinical significance of *BRCA* mutation status in ovarian cancer have produced conflicting results, especially regarding survival.

Objective To determine whether hereditary ovarian cancers have distinct clinical and pathological features compared with sporadic (nonhereditary) ovarian cancers.

Design and Setting Retrospective cohort study of a consecutive series of 933 ovarian cancers diagnosed and treated at our institution, which is a comprehensive cancer center as designated by the National Cancer Institute, over a 12-year period (December 1986 to August 1998).

Patients The study was restricted to patients of Jewish origin because of the ease of *BRCA1* and *BRCA2* genotyping in this ethnic group. From the 189 patients who identified themselves as Jewish, 88 hereditary cases were identified with the presence of a germline founder mutation in *BRCA1* or *BRCA2*. The remaining 101 cases from the same series not associated with a *BRCA* mutation and 2 additional groups (Gynecologic Oncology Group protocols 52 and 111) with ovarian cancer from clinical trials (for the survival analysis) were included for comparison.

Main Outcome Measures Age at diagnosis, surgical stage, histologic cell type and grade, and surgical outcome; and response to chemotherapy and survival for advanced-stage (III and IV) cases.

Results Hereditary cancers were rarely diagnosed before age 40 years and were common after age 60 years, with mean age at diagnosis being significantly younger for *BRCA1*- vs *BRCA2*-linked patients (54 vs 62 years; *P*=.04). Histology, grade, stage, and success of cytoreductive surgery were similar for hereditary and sporadic cases. The hereditary group had a longer disease-free interval following primary chemotherapy in comparison with the nonhereditary group, with a median time to recurrence of 14 months and 7 months, respectively (*P*<.001). Those with hereditary cancers had improved survival compared with the nonhereditary group (*P*=.004). For stage III cancers, *BRCA* mutation status was an independent prognostic variable (*P*=.03).

Conclusions Although *BRCA*-associated hereditary ovarian cancers in this population have surgical and pathological characteristics similar to those of sporadic cancers, advanced-stage hereditary cancer patients survive longer than nonhereditary cancer patients. Age penetrance is greater for *BRCA1*-linked than for *BRCA2*-linked cancers in this population.

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DATA FROM EPIDEMIOLOGIC and molecular genetic analyses indicate that about 10% of all epithelial ovarian carcinomas are associated with autosomal dominant genetic predisposition, conferred primarily by inherited mutations in *BRCA1* or *BRCA2*.[1] The *BRCA* genes function as classic tumor suppressors, with loss of function of both alleles required for tumorigenic progression. Evidence exists supporting a role for the *BRCA* proteins in the cellular response to specific forms of DNA damage,[2,3] and possibly in the transcriptional regulation of gene expression.[4-8] Tumor-suppressor defects in specific pathways of DNA repair and gene expression, vs general defective growth regulation, may be predicted to lead to malignancies with distinct molecular genetic, pathological, and clinical features. Studies on defining the somatic molecular[9] and cytogenetic[10] alterations present in *BRCA*-associated ovarian cancers support this hypothesis.

Studies on the clinical features of hereditary ovarian cancer have produced inconsistent findings, especially regarding survival. Ovarian cancers associated with germline *BRCA1* mutations were initially shown to have a significantly more favorable clinical course than matched sporadic cancers,[11] confirmed[12] or contradicted[13,14] by subsequent studies. In contrast, there is general agreement that *BRCA1*-associated

Author Affiliations: Departments of Surgery (Drs Boyd, Sonoda, Rhei, Maresco, Barakat, Brown, Chi, Curtin, Poynor, and Hoskins, Mr Federici, and Mss Bogomolniy and Almadrones), Human Genetics (Dr Boyd), and Pathology (Dr Saigo), Memorial Sloan-Kettering Cancer Center, New York, NY.

Corresponding Author and Reprints: Jeff Boyd, PhD, Department of Surgery, Box 201, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (e-mail: boydj@mskcc.org).

ovarian cancers are typically of serous histology, moderate to high grade, advanced stage, and diagnosed at a younger age compared with sporadic ovarian cancers.[11-14] Survival analysis in this context is difficult to perform in an unbiased fashion, as the relative ease of performing genetic typing of living patients vs that of deceased persons leads to introduction of an ascertainment bias favoring long-term survivors. Also, survival in advanced ovarian cancer is affected by the quality and type of surgery and chemotherapy treatments received, variables difficult to adequately control for in retrospective comparative studies. The most unbiased approach to this type of survival analysis requires the genotyping of a consecutive series of archival tissue specimens from a single institution, controlling for surgical and medical variables.

The purpose of this study was to test the hypothesis that hereditary ovarian cancers associated with germline mutations in *BRCA1* or *BRCA2* have distinct clinical and pathological characteristics compared with matched sporadic cases. Such data could provide insights into the biological function of *BRCA* proteins, the mechanism through which *BRCA*-linked cancers arise, and potential therapeutic strategies targeting *BRCA*-deficient cancers. To avoid ascertainment and treatment-related biases, the study subjects were retrospectively ascertained through genotyping of a consecutive series of ovarian cancers from 1 institution, all having received similar surgical and medical treatments.

METHODS
Subjects

A consecutive series of 933 cases of invasive epithelial ovarian carcinoma diagnosed and treated at this institution (a comprehensive cancer center as designated by the National Cancer Institute) from December 1986 to August 1998 were studied. Of these, for 189 patients, a religious preference of Jewish was indicated in the medical record. The study was restricted to patients of Jewish origin because of the relative ease of *BRCA1* and *BRCA*2 genotyping as a re-

sult of the existence of 3 common founder (ancient) mutations in this ethnic group (see below), and the relatively large fraction of ovarian cancer cases that are linked to *BRCA* in the Ashkenazim (45%-48%).[15,16] Archival pathological tissue specimens were accessioned from hospital tissue banks for each of the 189 cases. Clinical and pathological information, including age at diagnosis, date of primary surgery, residual disease following primary surgery (optimal or suboptimal), surgical stage, histologic cell type and grade, time to recurrence following chemotherapy, and clinical status at last follow-up were abstracted from hospital records. Tissue specimens and associated information were assigned a unique identifying number and made anonymous according to a protocol approved by the institutional review board of the Memorial Sloan-Kettering Cancer Center. All cases were genotyped, yielding 88 cases of *BRCA*-linked hereditary ovarian cancer and 101 cases without a *BRCA* mutation.

For survival analysis, 2 additional comparison groups from clinical trials were compared with our institutional comparison group. The first group consisted of 349 patients with stage III ovarian carcinoma and optimal cytoreductive surgery enrolled in both arms of Gynecologic Oncology Group protocol 52, a randomized trial of cisplatin and cyclophosphamide with or without doxorubicin.[17] The second group consisted of 386 patients with stage III or stage IV ovarian carcinoma and suboptimal cytoreductive surgery enrolled in both arms of Gynecologic Oncology Group protocol 111, a randomized trial of cisplatin with cyclophosphamide or paclitaxel.[18] Raw data for survival in these 2 clinical trials were provided by the Gynecologic Oncology Group Statistical Office (Buffalo, NY).

Genotyping

Genomic DNA was isolated from archival tissue specimens using standard protocols.[19] All cases were analyzed for the presence of 3 *BRCA* founder mutations common in the Ash-

kenazi Jewish population, 185delAG and 5382insC in *BRCA1*, and 6174delT in *BRCA2*.[20-22] Polymerase chain reaction products containing each mutation were generated with the primers 5′-TCTGCTCTTCGCGTT-GAAGAA-3′ and 5′-CACTCTTGTGC-TGACTTACCA-3′ for *BRCA1* 185delAG (90–base pair [bp] product); 5′-CAGCATGATTTTGAAGT-CAG-3′ and 5′-AGGGAGCTT-TACCTTTCTGTC-3′ for *BRCA1* 5382insC (99-bp product); and 5′-GGGAAGCTTCATAAGTCAGTC-3′ and 5′-TTTGTAATGAAGCATCT-GATACC-3′ for *BRCA2* 6174delT (97-bp product). Radiolabeled products were produced using a forward primer end-labeled with $[\gamma\text{-}^{33}\text{P}]$ adenosine triphosphate, then visualized by denaturing polyacrylamide gel electrophoresis followed by autoradiography as previously described.[23] All mutations were confirmed by independent polymerase chain reaction amplification of the corresponding DNA sample and direct sequence analysis of the product as described.[9] All mutations were confirmed as germline through analysis of DNA from nontumor tissue from each case. Of the 88 ovarian cancer cases associated with 1 of the deleterious *BRCA* mutations, 67 were linked to *BRCA1* (51 with 185delAG and 16 with 5382insC) and 21 to *BRCA2*. The additional 101 ovarian cancer patients from this series who did not carry 1 of these mutations comprised the institutional comparison group.

Data and Statistical Analyses

A total of 189 cases of invasive epithelial ovarian cancer were identified from this consecutive series of cases, which were from a single institution; all patients were self-described as Jewish and were categorized according to presence (hereditary cases) or absence (sporadic cases) of a germline *BRCA* mutation. The patients in both groups received similar ovarian cancer therapies at this institution of primary cytoreductive surgery followed by chemotherapy. The standard primary chemotherapeutic regimen for advanced-stage ovarian cancer

at this institution is combination therapy, involving cisplatin and cyclophosphamide prior to 1993 and cisplatin and paclitaxel from 1993 to the present. Similar fractions of both groups were treated during these periods (**TABLE 1**). The date of initial surgery was used as the date of diagnosis. It also was used to calculate survival according to date of death or most recent follow-up if still alive. Surgical stage and histologic grade and cell type were categorized according to Inter-

national Federation of Gynecology and Obstetrics and World Health Organization standards and were obtained from pathology reports and operative notes in the medical record. In cases in which histologic grade or cell type was reported as mixed, categorization was based on the predominant pattern. For categorization of the results of primary cytoreductive surgery, a definition of optimal was used for residual disease less than 2 cm, and suboptimal for residual disease greater than or equal to 2 cm. Recurrence-free interval was estimated as the time from initiation of primary chemotherapy to the initiation of salvage chemotherapy, or to the date of last follow-up if disease-free.

Cumulative survival and recurrence-free interval probabilities (which were analyzed for advanced-stage [III and IV] cancers) were calculated by the Kaplan-Meier method.[24] For univariate comparisons of survival between groups, statistical significance was assessed using the Cox-Mantel test.[25] Multivariate regression analyses were performed using the Cox proportional hazards model; this model was deemed appropriate after assessing the time dependence of the hazard ratio. For the multivariate analysis of advanced-stage disease, stage III was considered separately from stage IV because of greater clinical importance. Statistical significance of differences between groups in age at diagnosis was determined via the 2-tailed t test, and of differences in the extent of surgical cytoreduction by the 2-tailed χ^2 test. Differences associated with $P<.05$ were considered statistically significant. Statistical analyses and significance tests were performed with the StatView (SAS Institute Inc, Cary, NC) and S-PLUS (MathSoft Inc, Cambridge, Mass) computer programs.

RESULTS

Clinical and pathological characteristics of hereditary and sporadic ovarian cancer groups are shown in Table 1. The age range for hereditary cases was 31 to 79 years and 25 to 87 years for sporadic cases. The average age at diagnosis was significantly younger for the

BRCA-associated cases vs sporadic cases ($P<.001$); a more detailed analysis of age characteristics is presented in **TABLE 2**. The mean age at diagnosis for BRCA1-associated cancers was 8 years younger than that for BRCA2-associated cancers ($P=.04$). For hereditary cancers, diagnosis before age 40 years was generally rare, and no cancers were seen in women younger than 30 years. Diagnosis in women older than 60 years was relatively common, and 16% of the hereditary cancers in this series were diagnosed at ages older than 70 years.

With regard to surgical and pathological features, the BRCA-associated cases were not significantly different from sporadic cases. Most tumors in this series were of advanced stage, serous histology, and moderate to poor differentiation. There were no well-differentiated tumors or tumors of mucinous histology seen in the hereditary group, and optimal cytoreduction was more common in the hereditary than in the sporadic group, but these differences were not statistically significant. Overall, the characteristics of both hereditary and sporadic cases in these clinical and pathological categories were generally similar to those observed for all invasive epithelial ovarian cancers.[26]

To determine whether the response to primary chemotherapy was different in BRCA-associated than in sporadic cases, probabilities for recurrence-free intervals between initial chemotherapy and salvage therapy were calculated for each patient with advanced-stage (III and IV) cancer in both groups, with 81 in the BRCA-associated group and 100 in the sporadic group. The hereditary cases had a significantly longer disease-free interval following initial chemotherapy than the sporadic cases, with a median time to recurrence of 14 months and 7 months, respectively ($P<.001$) (**FIGURE 1**).

In analyses of cumulative survival probabilities, advanced-stage BRCA-associated cases survived significantly longer than advanced-stage sporadic cases (**FIGURE 2**, A) ($P=.004$). When hereditary cases were analyzed separately, BRCA1-linked cases survived significantly longer than sporadic cases

Table 1. Clinical and Pathological Features of Ovarian Cancers*

Variable	BRCA-Associated	Sporadic
No. of subjects	88	101
No. alive at time of analysis	39 (44)	37 (37)
Length of follow-up, mean (median), mo†	41 (57)	37 (59)
Age, mean (SD), y	56 (11)	63 (12)
Stage		
I	3 (3)	0
II	4 (5)	1 (1)
III	68 (77)	86 (85)
IV	13 (15)	14 (14)
Grade		
1	0	6 (6)
2	18 (20)	16 (16)
3	70 (80)	79 (78)
Histologic characteristics		
Serous	60 (68)	61 (60)
Endometrioid	12 (14)	13 (13)
Clear cell	2 (2)	7 (7)
Mucinous	0	5 (5)
Other	2 (2)	3 (3)
Adenocarcinoma‡	12 (14)	12 (12)
Primary surgery		
Optimal	51 (58)	45 (45)
Suboptimal	37 (42)	56 (55)
Chemotherapy		
Cisplatin/ cyclophosphamide	49 (56)	66 (65)
Cisplatin/paclitaxel	39 (44)	35 (35)

*Values are expressed as number (percentage) unless otherwise indicated.
†Follow-up refers to time from date of initial surgery to date of death or to most recent follow-up visit for persons alive at time of analysis.
‡Not otherwise specified.

Table 2. Age at Diagnosis for BRCA-Associated and Sporadic Ovarian Cancers

	Hereditary		Sporadic (n = 101)
Variable	BRCA1 (n = 67)	BRCA2 (n = 21)	
Age at diagnosis, mean (SD), y	54 (11)	62 (10)	63 (12)
Range, y	31-79	44-77	25-87
No. (%) of subjects by age group, y			
≤30	0	0	1 (1)
31-40	4 (6)	0	2 (2)
41-59	35 (53)	5 (24)	26 (26)
60-69	19 (28)	11 (52)	38 (38)
≥70	9 (13)	5 (24)	34 (34)

(Figure 2, B) (P = .008), and although *BRCA2*-linked cases displayed a trend toward longer survival (Figure 2, C), this difference did not achieve statistical significance (P = .09). With regard to the 2 distinct mutations within the *BRCA1* group, there was no significant difference in survival between patients with the 185delAG mutation vs those with the
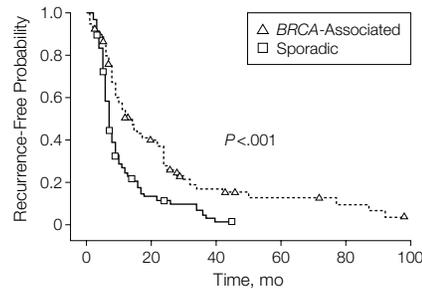
Figure 1. Recurrence-Free Interval Probabilities in Patients With Advanced-Stage (III and IV) *BRCA*-Associated (n = 81) and Sporadic (n = 100) Ovarian Cancers

Symbols represent time to most recent follow-up in recurrence-free patients.

Figure 2. Cumulative Survival Probabilities in Patients With Advanced-Stage (III and IV) *BRCA*-Associated and Sporadic Ovarian Cancers

A, All *BRCA*-linked cases (n = 81) vs sporadic cases (n = 100). B, *BRCA1*-linked cases (n = 61) vs sporadic cases (n = 100). C, *BRCA2*-linked cases (n = 20) vs sporadic cases (n = 100). D, All stage III and IV *BRCA*-linked cases (n = 81), stage III patients from Gynecologic Oncology Group (GOG) protocol 52 (n = 349), institutional stage III and IV sporadic cases (n = 100), and stage III and IV patients from GOG protocol 111 (n = 386). Symbols represent time to most recent follow-up in surviving patients. Note variation in scale of x-axes.

5382insC mutation (P = .40), although there may be inadequate power to detect a difference. The number of patients in the hereditary and sporadic groups alive at the time of analysis and the mean and median lengths of follow-up for persons alive at analysis in each group since time of initial surgery are shown in Table 1.

To determine whether survival in our institutional comparison group of sporadic cases was representative of that in a larger ovarian cancer population, we compared survival in the advanced-stage cases in our sporadic group with that in 2 groups of advanced-stage ovarian cancer clinical trial patients treated with comparable surgical and chemotherapeutic regimens. One group consisted of patients with suboptimally cytoreduced, stage III and IV disease (Gynecologic Oncology Group protocol 111) and the other consisted of patients with optimally cytoreduced, stage III disease (Gynecologic Oncology Group protocol 52). The institutional comparison group consisted of a

combination of optimally and suboptimally cytoreduced patients and showed a survival trend intermediate between that of the 2 clinical trial groups that was not significantly different from either (Figure 2, D).
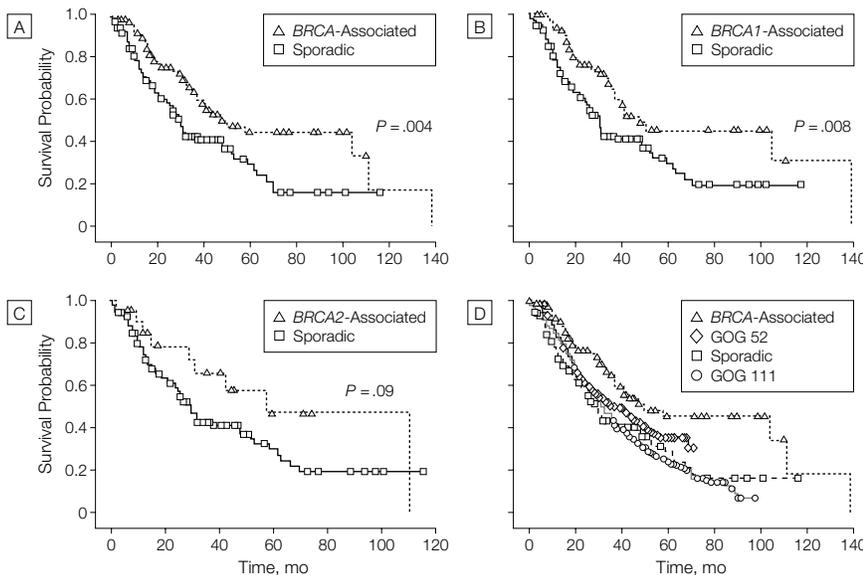
In univariate analyses of the clinical and pathological factors studied, age at diagnosis (as a continuous variable), extent of surgical cytoreduction (optimal vs suboptimal), and *BRCA* mutation status (mutation vs no mutation) achieved statistical significance as prognostic variables for the 88 *BRCA*-associated and 101 sporadic cases and were included in a multivariate analysis (**TABLE 3**). For stage III cases (81% of the total patients), the presence of a germline *BRCA* mutation was a significant independent prognostic variable (P = .03), conferring a 25% decrease in relative risk of death vs sporadic cases after adjusting for age and extent of surgical cytoreduction. When including patients with early stage and stage IV disease, age and surgical cytoreduction were statistically significant as independent prognostic factors (P < .01 for both), with *BRCA* mutation status of borderline significance (P = .05).

COMMENT

These data support the hypothesis that *BRCA*-associated hereditary ovarian can-

Table 3. Multivariate Analysis for Predictors of Survival

Variable	Hazard Ratio (95% Confidence Interval)	*P* Value
Stage III cases (n = 154)*		
BRCA mutation†	0.75 (0.58-0.97)	.03
Age‡	1.03 (1.01-1.05)	.01
Surgery§	1.48 (1.18-1.86)	.01
All cases (n = 189)		
BRCA mutation	0.79 (0.63-1.00)	.05
Age	1.03 (1.01-1.05)	<.01
Surgery	1.37 (1.12-1.68)	<.01

*For the multivariate analysis of advanced-stage disease, stage III was considered separately from stage IV because of greater clinical importance.
†Relative death rate of *BRCA* mutation carriers vs that of noncarriers, after adjusting for age at diagnosis and outcome of primary surgery.
‡Relative increase in the death rate for each increasing year of age at diagnosis adjusted for *BRCA* mutation status and outcome of primary surgery.
§Relative death rate of those patients with suboptimal cytoreduction vs that of patients with optimal cytoreduction adjusted for *BRCA* mutation status and age at diagnosis.

cers have a distinct clinical behavior compared with sporadic ovarian cancers. We used an ascertainment strategy designed to avoid 2 common sources of bias in a study of this type. First, by retrospective identification of all cases from a consecutive series of ovarian cancers, using archival specimens, selection bias resulting from preferential inclusion of living patients in the hereditary group was avoided. Second, differences in outcome related to treatment were minimized by analysis of hereditary and sporadic ovarian cancer groups diagnosed and treated at a single institution over the same period.

Other strengths of the study design include the analysis of Jewish patients positive and negative for *BRCA* founder mutations, which strengthens the reliability of hereditary vs sporadic categorization. All 3 mutations are clearly deleterious, and Jewish persons without 1 of these 3 mutations are unlikely to have undetected *BRCA* mutations.[27] Although there have been a small number of case reports of Jewish persons with *BRCA* variants other than the 3 founder mutations,[28-30] the presence of a low fraction of hereditary cases in the sporadic group would only bias the data toward the null hypothesis. The identification of *BRCA*-associated ovarian cancer cases without regard to family or medical history provides several important insights into the clinical manifestation of hereditary ovarian cancer not realized by ascertainment using traditional strategies (eg, identification through early age at diagnosis, family history of breast or ovarian cancer, or prior breast cancer history).

Data related to age at diagnosis for hereditary cases have important implications for genetic counseling and clinical decision making. The age penetrance for *BRCA1* was significantly greater than for *BRCA2* (ie, earlier age at diagnosis), consistent with estimates derived from analyses of breast and ovarian cancer families, suggesting that ovarian cancer penetrance generally is higher for *BRCA1* than for *BRCA2*.[31-34] In fact, the mean age at diagnosis for *BRCA2*-associated cancers was not significantly different from that of the sporadic group

in this study, or from that of all invasive ovarian cancers.[26] The *BRCA*-associated ovarian cancers were not seen in women younger than 30 years, and were rarely diagnosed when women were younger than 40 years. In contrast, the hereditary cancers in this series were commonly diagnosed between ages 60 and 69 years, 52% linked to *BRCA2* and 28% to *BRCA1*. Sixteen percent of all *BRCA*-associated cancers were diagnosed in women older than 70 years. Regarding issues related to prophylactic oophorectomy for asymptomatic *BRCA* heterozygotes, these data suggest that a substantial period exists during young adulthood when fertility may be preserved, and that an increased risk of ovarian cancer persists well after age 60 years, especially for *BRCA2* carriers. Age at diagnosis was found to be an independent prognostic factor by multivariate analysis in this study. While younger age is recognized as a favorable prognostic variable in ovarian cancer, this association has traditionally been attributed to the prevalence of borderline tumors, earlier stages, more favorable histologic features, and a higher frequency of optimal cytoreduction in younger patients.[35]

Other pathological and surgical characteristics of the *BRCA*-associated tumors were not significantly different from those of the institutional comparison group or from all invasive epithelial ovarian cancers generally. No well-differentiated tumors were observed in the *BRCA* group, and the absence of mucinous tumors is consistent with prior observations regarding the underrepresentation of this histologic cell type and the prevalence of serous cancers in a hereditary context.[11,36-40] Nearly all of the tumors were of advanced stage at the time of diagnosis, although it is noteworthy that invasive stage I and stage II cancers were observed in the *BRCA* group, supporting the impression that hereditary ovarian cancers have a natural history similar to that of sporadic cancers, and may be amenable to early diagnosis. The *BRCA*-associated cancers were more likely than those in the institutional comparison group to be optimally cytoreduced at primary surgery,

although this difference was not statistically significant; however, all of the advanced-stage cancers in the hereditary group presented with a tumor volume of greater than 2 cm, so that those categorized as optimally cytoreduced were rendered so surgically, rather than as a result of low-volume disease (<2 cm) at presentation. Thus, the hereditary tumors do not appear unique in terms of tumor volume or the extent of disease at diagnosis. Not unexpected was the finding that the extent of primary surgical cytoreduction, a well-established prognostic factor for advanced-stage ovarian cancer,[28] was also an independent prognostic variable in this study.

Analysis of survival in advanced-stage patients revealed that *BRCA*-associated cases survived significantly longer than sporadic cases, supporting prior reports of this phenomenon in *BRCA1*-linked ovarian cancers that were analyzed using a less-rigorous study design.[11,12] By multivariate analysis, *BRCA* mutation status was an independent predictor of survival for advanced-stage ovarian cancers. Furthermore, our analyses suggest that this survival advantage is likely to apply to both *BRCA1*-linked and *BRCA2*-linked subgroups of hereditary ovarian cancer when considered separately, although a larger series will be required to strengthen the statistical significance of the *BRCA2*-related survival association. Validity of these findings is strengthened by the representative behavior of our institutional comparison group, which displayed survival characteristics similar to those seen in 2 large clinical trials for advanced-stage ovarian cancer. The prevalence of *BRCA* mutations in persons in these trial groups is unknown but could be as high as 10%.[1] Discrepancies in the results of published studies of survival in *BRCA*-associated ovarian cancer may be related to the stage of disease compared. In all 3 studies[11,12] (including this article) reporting a survival advantage for hereditary cancers, the analyses were based on advanced-stage cases, while those reporting no difference or a worse prognosis for hereditary cancers[13,14] examined cases without stratifying for

stage. In contrast to our data, the literature on survival or disease recurrence in *BRCA*-linked breast cancers has shown no consistent difference from that in the sporadic breast cancer population. However, given that *BRCA*-linked breast cancers clearly exhibit a number of histopathological and molecular genetic features typically associated with a poorer prognosis, such as high grade, high proliferative index, estrogen receptor negativity, aneuploidy, and somatic p53 inactivation,[41] the fact that survival is similar may suggest that response to chemotherapy is actually improved.

There are at least 2 possible explanations for the longer survival in *BRCA*-associated ovarian cancers. Although these cancers present with surgical and pathological characteristics remarkably similar to those of sporadic ovarian cancers, the underlying biological properties of the hereditary tumors, as yet undefined, may lead to a more indolent clinical behavior through, for example, a slower rate of cell division. Alternatively, the hereditary tumors may respond more favorably to chemotherapy, a possibility consistent with our finding that *BRCA*-associated cancers display a longer recurrence-free interval following primary chemotherapy. This scenario is also predicted by current knowledge pertaining to the likely molecular function of *BRCA* proteins; both are believed to participate in 1 or more pathways of DNA damage recognition or repair, and their inactivation would predictably result in a greater sensitivity of *BRCA*-deficient ovarian cancer cells to cytotoxic agents, which act through the induction of damage. If ovarian cancers associated with *BRCA* mutations are in fact more susceptible to therapeutic agents that induce a particular form of DNA damage, double-strand breaks for example, then this patient population may prove even more responsive to selected chemotherapeutic agents that induce that type of DNA damage. The direct testing of this hypothesis in the laboratory is expected to lead to further insights into the function of *BRCA* gene products and improved clinical strategies for the treatment of this subset of patients with advanced-stage ovarian cancer.

REFERENCES

1. Boyd J. Molecular genetics of hereditary ovarian cancer. *Oncology (Huntingt).* 1998;12:399-406.
2. Brugarolas J, Jacks T. Double indemnity: p53, *BRCA* and cancer. *Nat Med.* 1997;3:721-722.
3. Zhang H, Tomblyn G, Weber BL. *BRCA1*, *BRCA2*, and DNA damage response. *Cell.* 1998;92:433-436.
4. Chapman MS, Verma IM. Transcriptional activation by *BRCA1*. *Nature.* 1996;382:678-679.
5. Monteiro AN, August A, Hanafusa H. Evidence for a transcriptional activation function of *BRCA1* C-terminal region. *Proc Natl Acad Sci U S A.* 1996;93:13595-13599.
6. Milner J, Ponder B, Hughes-Davies L, et al. Transcriptional activation functions in *BRCA2*. *Nature.* 1997;386:772-773.
7. Scully R, Anderson SF, Chao DM, et al. *BRCA1* is a component of the RNA polymerase II holoenzyme. *Proc Natl Acad Sci U S A.* 1997;94:5605-5610.
8. Gowen LC, Avrutskaya AV, Latour AM, et al. *BRCA1* required for transcription-coupled repair of oxidative DNA damage. *Science.* 1998;281:1009-1012.
9. Rhei E, Bogomolniy F, Federici MG, et al. Molecular genetic characterization of *BRCA1*- and *BRCA2*-linked hereditary ovarian cancers. *Cancer Res.* 1998;58:3193-3196.
10. Tapper J, Sarantaus L, Vahteristo P, et al. Genetic changes in inherited and sporadic ovarian carcinomas by comparative genomic hybridization. *Cancer Res.* 1998;58:2715-2719.
11. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathologic features of ovarian cancer in women with germ-line mutations of *BRCA1*. *N Engl J Med.* 1996;335:1413-1416.
12. Aida H, Takakuwa K, Nagata H, et al. Clinical features of ovarian cancer in Japanese women with germline mutations of *BRCA1*. *Clin Cancer Res.* 1998;4:235-240.
13. Johannsson OT, Ranstam J, Borg A, Olsson H. Survival of *BRCA1* breast and ovarian cancer patients. *J Clin Oncol.* 1998;16:397-404.
14. Pharoah PD, Easton DF, Stockton DL, et al. Survival in familial, *BRCA1*-associated, and *BRCA2*-associated epithelial ovarian cancer. *Cancer Res.* 1999;59:868-871.
15. Beller U, Halle D, Catane R, et al. High frequency of *BRCA1* and *BRCA2* germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. *Gynecol Oncol.* 1997;67:123-126.
16. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder *BRCA1* and *BRCA2* mutations in Ashkenazi Jews in Israel. *Am J Hum Genet.* 1997;60:1059-1067.
17. Omura GA, Bundy BN, Berek JS, et al. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma. *J Clin Oncol.* 1989;7:457-465.
18. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334:1-6.
19. Strauss WM. Preparation of genomic DNA from mammalian tissue. In: Ausubel FM, Brent R, Kingston RE, et al, eds. *Current Protocols in Molecular Biology.* Vol 1. New York, NY: John Wiley & Sons; 1998:2.2.1-2.2.3.
20. Struewing JP, Abeliovich D, Peretz T, et al. The carrier frequency of the *BRCA1* 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat Genet.* 1995;11:198-200.
21. Oddoux C, Struewing JP, Clayton CM, et al. The carrier frequency of the *BRCA2* 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet.* 1996;14:188-190.
22. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in *BRCA1* and *BRCA2*. *Nat Genet.* 1996;14:185-187.
23. van der Heijden O, Chiu H-C, Park T-C, et al. Allelotype analysis of uterine leiomyoma. *Mol Carcinog.* 1998;23:243-247.
24. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
25. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966;50:163-170.
26. Ozols RF, Rubin SC, Thomas G, Robboy S. Epithelial ovarian cancer. In: Hoskins WJ, Perez CA, Young RC, eds. *Principles and Practice of Gynecologic Oncology.* Philadelphia, Pa: Lippincott-Raven; 1997:919-986.
27. Shattuck-Eidens D, Oliphant A, McClure M, et al. *BRCA1* sequence analysis in women at high risk for susceptibility mutations. *JAMA.* 1997;278:1242-1250.
28. Randall TC, Bell KA, Rebane BA, et al. Germline mutations of the *BRCA1* and *BRCA2* genes in a breast and ovarian cancer patient. *Gynecol Oncol.* 1998;70:432-434.
29. Robson ME, Offit K. New *BRCA2* mutation in an Ashkenazi Jewish family with breast and ovarian cancer. *Lancet.* 1997;350:117-118.
30. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of *BRCA1* and *BRCA2*. *J Clin Oncol.* 1998;16:2417-2425.
31. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer. *Am J Hum Genet.* 1993;52:678-701.
32. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. *Am J Hum Genet.* 1995;56:265-271.
33. Narod SA, Ford D, Devilee P, et al. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. *Am J Hum Genet.* 1995;56:254-264.
34. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. *Am J Hum Genet.* 1998;62:676-689.
35. Friedlander ML, Dembo AJ. Prognostic factors in ovarian cancer. *Semin Oncol.* 1991;18:205-212.
36. Bewtra C, Watson P, Conway T, et al. Hereditary ovarian cancer. *Int J Gynecol Pathol.* 1992;11:180-187.
37. Piver MS, Baker TR, Jishi MF, et al. Familial ovarian cancer. *Cancer.* 1993;71(2 suppl):582-588.
38. Narod S, Tonin P, Lynch H, et al. Histology of *BRCA1*-associated ovarian tumours. *Lancet.* 1994;343:236.
39. Narod SA, Madlensky L, Bradley L, et al. Hereditary and familial ovarian cancer in southern Ontario. *Cancer.* 1994;74:2341-2346.
40. Zweemer RP, Verheijen RH, Gille JJ, et al. Clinical and genetic evaluation of thirty ovarian cancer families. *Am J Obstet Gynecol.* 1998;178(1 pt 1):85-90.
41. Robson M, Levin D, Federici M, et al. Breast conservation therapy for invasive breast cancer in Ashkenazi women with *BRCA* gene founder mutations. *J Natl Cancer Inst.* 1999;91:2112-2117.